Glyphosate: Cancer Assessment

Overview

* History
* IARC
* New Data
* CARC Re-Evaluation
* IARC/CARC differences

History

* 1985 – Group C Carcinogen; Possible Human Carcinogen
  * Male mouse kidney tumors (**adenomas only**) – 0/50 controls; 0/50 low; 1/50 mid and 3/50 high dose
  * No evidence of carcinogenicity in female mice or male/female rats
* PWG – Evaluation of additional kidney slides of all treated groups
  * Adenomas: 1/49; 0/50; 0/50; 1/50
  * Carcinomas: 0/49; 0/50; 1/50; 2/50
  * Tumors Not Treatment- Related- No trend or pairwise statistical significance; no preneoplastic lesions; lack of multiple tumors;
* 1986 – SAP Evaluation
  * Group D Chemical; Not Classifiable to Human carcinogenicity
  * Renal tumors equivocal, mainly adenomas, no statistical significance. Recommended a DCI for repeat mouse and rat studies

History

- **1991 CPRC Review**
- Group C: Carcinogen; Possible Human Carcinogen
  - Equivocal (kidney) tumor response in male mice
  - Lack of statistical significance – pairwise
  - No pre-neoplastic lesions
  - Magnitude of response poor 3/50 @ very high dose (4945 m/k/d)
  - No evidence of carcinogenicity in female mice, male or female rats
  - No mutagenicity/genotoxicity concerns
  - No SAR concerns

IARC Evaluation - 2015

* Group 2A- Probable Human Carcinogen (Group 2A)
  * **Limited Evidence in Humans**
    * Positive association for Non-Hodgkin Lymphoma
    * Case-control – Canada
    * Case-control- Sweden
    * Case- control – Sweden (follow-up study)
    * Case-control – U.S.A
  * **Sufficient Evidence in Animals**
    * Positive trend for renal carcinoma and combined adenoma/carcinoma in male mice in one study
    * Positive trend for hemangiosarcomas in male mice in the second study
  * **Strong evidence for genotoxicity**
    * Glyphosate and glyphosate-formulations
    * DNA and chromosomal damage in mammals *in vivo* and in humans and animals *in vit*ro.

New Data Evaluated in 2015

* 1991 CPRC Data Set
  * 1 Mouse and 2 Rat carcinogenicity studies submitted to OPP
  * Mutagenicity studies submitted to OPP
* IARC Data Set
  * 28 Epidemiology studies
  * 2 Mouse carcinogenicity studies (1 study submitted to JMPR but not to OPP)
  * 4 Rat carcinogenicity studies (2 studies submitted to JMPR but not to OPP)
  * Mutagenicity studies in the published literature
* 2015 CARC Data Set
  * 31 Epidemiology studies
  * 4 Mouse cancer studies (1 more mouse study rejected due to viral infection)
  * 7 Rat cancer studies (1 more rat study rejected due to lack of purity data)
  * 54 Mutagenicity studies

Note: 5 Studies cited in Griem *et al* 2015 review article not evaluated by IARC

http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

CARC Evaluation

* 2005 Cancer Guidelines: "Not Likely to be Carcinogenic to Humans"
* Evidence in Humans
  * No association between glyphosate exposure and cancer of: the oral cavity; esophagus, stomach; colon; rectum; colorectum; lung; pancreas; kidney; bladder; prostate; breast; cutaneous melanoma; or soft tissue sarcoma
  * No association between glyphosate exposure and brain cancer (gliomas); leukemia oar multiple myeloma
  * Inconclusive for a causal or clear associative relationship between glyphosate exposure and NHL
    * No association in 5 case-control and 1 prospective cohort studies
    * Suggestive association in 2 case-control studies in Sweden
    * Limitations for most of these studies include: small sample size; limited power; no quantitative exposure data; no blood biomarkers (interview by questionnaires); no knowledge of product used (formulations); risk ratios with large CIs; and recall bias as well as missing data.
  * The literature will continue to be monitored for studies related to glyphosate and risk of NHL.

CARC Evaluation (continued)

* **Evidence in Animals**
* No evidence of carcinogenicity in 4 studies with CD-1 mice following dietary administration at doses ranging from 85.0 to 4945 mg/kg/day for up to 2 years
* No evidence of carcinogenicity in 7 studies in Sprague Dawley or Wistar rats following dietary administration at doses ranging from 3.0 to 1500 mg/kg/day for up to 2 years
* **Evidence for Mutagenicity**
* No mutagenic or genotoxic concern in a wide range of *in vivo* and in vitro assays: negative for gene mutation, chromosomal damage, DNA damage and repair

Epidemiology Studies: IARC and CARC

* IARC: Limited Evidence in Humans based on increased risk for NHL (4 studies)
* CARC: Epidemiologic studies does not support causal association.

1. **Case-control - Canada**: 51 exposed cases/133 controls (McDuffie *et al*. 2001)

IARC: Positive association only for those with more than 2/days/year exposure.

CARC: Increase not statistically significant (OR=1.20; 95% CI=0.87-1.8) and No adjustment made for exposure from use of other pesticides.

Note: IARC only used the ≥2 days data and not the negative association ≤ 2 days exposure

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2. **Case-Control - Sweden**: 8 exposed/8 controls (Hardell *et al*. 2002)

IARC: Excess risk based on pooled analysis of 2 studies [NHL and HCL (a NHL variant)].

CARC: The excess risk (OR= 3.04; 95% CI=1.08 – 8.52) in a univariate analysis declined when study site, vital status, and exposure to other pesticides were taken into a multivariate analysis (OR=1.85; 95% CI=0.55-6.20)

Note: Few exposed cases; individual studies non-significant; large CI.

Epidemiology Studies: IARC and CARC

3. **Case-control – U.S.A**: 36 exposed/61 controls (De Roos *et al*. 2003)

IARC: Increase in logistic regression analysis (OR=2.1; 95% CI= 1.1- 4.0)

CARC: Non significant in the hierarchical regression (OR=1.6; 95% CI=0.9–2.8)

Note: IARC used the logistic analysis in their rationale, but not the hierarchical analysis which is used to adjust for exposure to other pesticides,

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4. **Case-control – Sweden**: 29 cases/18 controls (Eriksson *et al*. 2008)

IARC: Increase in univariate (OR=2.02; 95% CI=1.10-3.71) and multivariate analysis (OR=1.51; 95% CI=0.77-2.94)

CARC: Suggestive; statistical significance only in univariate but not in multivariate

Note: IARC noted the non-significance but included in their rationale.

Lack of dose-response; imprecise risk estimates with wide CI; no consistent pattern; recall bias; multiple exposures; does not support causal association

Animal Studies: IARC and CARC

IARC: Identifies "hazard" according to its "Preamble"

* The IARC assessment looks at the intrinsic **'hazard'** of a chemical as a cancer-causing agent only. Other components of the toxicity of the chemical are not taken into account.
* IARC reviews only reports/studies published in the open literature.
* Preamble: "*sufficient evidence of carcinogenicity*" based on the occurrence of increased tumors (benign, malignant, or combination) in:
  * 1) two or more species of animals;
  * 2) **two or more independent studies in one species; a**nd/or
  * 3) an increased incidence of tumors in both sexes of a single species

Animal Studies: IARC and CARC

* EPA: Weight-of-Evidence Approach (2005 Guidelines):
* tumors in multiple species, strains, or both sexes;
* dose-response;
* progression of lesions from pre-neoplastic to benign to malignant;
* proportion of malignant tumors;
* reduced latency of neoplastic lesions;
* both biological and statistical significance of the findings;
* use of the background incidence (historical control) data;

Animal Studies: IARC and CARC

Male Mouse Kidney Tumor (MRID No.00251007)

PWG Read: Fisher's Exact & Exact Trend Test				
Tumor Type	0 mg/kg/day	161 mg/kg/day	835 mg/kg/day	4945 mg/kg/day
Adenomas *P* =	1/49 (2%) 0.4422	0/49 (0%) 1.0000	0/50 (0%) 1.00000	1/45 (2%) 0.7576
Carcinomas *P* =	0/49 (0%) 0.0635	0/49 (0%) 1.0000	1/50 (2%) 0.5051	2/50 (4%) 0.2525
Combined *P* =	1/49 (2%) 0.0648	0/49 (0%) 1.0000	1/50 (2%) 0.7576	3/50 (6%) 0.3163

IARC: Positive trend for carcinoma (P=0.037) and adenoma/carcinoma (P=0.034) - Cochran-Armitage trend test

CARC: Not treatment-related based on:

- No positive trend or pair-wise significance;
- No pre-neoplastic lesions;
- Low magnitude of response – 4x the Limit Dose;
- Incidences within historical control range; and

Animal Studies: IARC and CARC

Male Mouse Hemangiosarcomas (MRID No.49631702)

Fisher's Exact Test and Exact Trend Test Results				
Dose (mg/kg/day)	0	100	300	1000
Hemangiosarcomas	0/47 (0%)	0/46 (0%)	0/50 (0%)	4/45 (9%)
P =	0.00296**	1.00000	1.00000	0.05332

IARC: Positive trend for hemangiosarcomas (P=0.001; Cochran-Armitage)

CARC: Not treatment-related based on:

- Tumors seen only at the limit dose;
- No pair-wise significance;
- Incidences was near or the same as the upper limit (0-8%);
- Not seen in male mice in the same strain in the other 3 studies;
- Considerable inter-group variability in incidences in female mice;
- Both spontaneous and treatment-related tumors arising from endothelial cells;
- Appear in both sexes but are generally more common in males; and
- As vascular tumors, they can occur at different sites

Mutagenicity: IARC and CARC

IARC:

There is strong evidence that exposure to glyphosate or glyphosate based formulations is genotoxic.

Data set included:

* Studies that tested glyphosate-formulated products;
* Studies where the test material was not well-characterized (*i.e.*, no purity information was provided).
* Focused on DNA damage as an endpoint (*e.g.*, comet assay);
* Studies with limitations confounding interpretation or results
* Many negative studies cited by Kier and Kirkland (2013) but were not included in the IARC decision

Mutagenicity: IARC and CARC

CARC:

No concern for mutagenicity or genotoxicity *in vivo* and *in vitro*. Negative for gene mutation, chromosomal damage, DNA damage and repair

- Glyphosate was not mutagenic in bacteria or mammalian cells *in vitro*
- Did not induce chromosomal aberrations *in vitro*.
- Although some studies in the open literature reported positive findings for micronuclei induction in rodents, these findings were not replicated in the majority of the rodent micronucleus assay studies.
- There is no convincing evidence that the DNA damage is a direct effect of glyphosate, but under some conditions may be secondary to cytotoxicity or oxidative damage.

Summary

Epidemiological Studies

* No association between glyphosate exposure and site-specific cancer
* Case-control studies on NHL: Does no support a direct causal association
* Prospective cohort (AHS) study on NHL: No significant increased risk

Experimental Animals

* No evidence of carcinogenicity in male or female mice in 4 studies
* No evidence of carcinogenicity in male or female in 2 strain of rats in 7 studies

Mutagenicity

* No concern for mutagenicity/genotoxicity *in vitro* or *in vivo*

Classification: Not Likely to be Carcinogenic to Humans

Around the World with Glyphosate

* **Australia (2013):** Currently, the weight and strength of evidence does not support the conclusion that glyphosate causes cancer in either laboratory animals or humans (APVMA, 07/2013).
* **Canada** (2015): No evidence of carcinogenicity in mice and rats (PRVD 2015-XX)
* **EU Regulation (CLP):** No classification
* **EFSA (2014):** Glyphosate does not show carcinogenic or mutagenic properties.
* **Germany (2014)**: Available data do not show carcinogenic or mutagenic properties of glyphosate.
* **JMPR/WHO (2004):** No evidence of carcinogenicity in rats or mice
* **Republic of California**: California's Environmental Protection Agency (Cal/EPA) intends to list the herbicide glyphosate – the active ingredient in Monsanto's RoundUp – as a carcinogenic chemical under the Proposition 6
* **South Africa**: Based on current risk assessments, glyphosate poses a minimal risk to users and the general public, provided it is used according to label instructions and safety statements.